The ramifications of HLA-B27

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Thirty years after its discovery,[1,2] the association between HLA-B27 and ankylosing spondylitis remains the strongest known relationship between a major histocompatibility complex (MHC) antigen and a disease.

Epidemiological studies in the 1960s and early 1970s identified close links between several distinct forms of arthritis that were given the collective title of the seronegative spondarthritides.[3] Recognition that HLA-B27 was a genetic marker for these diseases led to a review of the composition of the group, resulting in the exclusion of Whipple's disease and Behçet's syndrome and the inclusion of other conditions such as undifferentiated and *formes frustes* of spondarthritis[4] and HLA-B27 associated isolated peripheral enthesitis.[5] Notwithstanding a 28–44% prevalence of HLA-B27 in affected patients, Whipple's disease was excluded after being found to be caused by the actinobacterium *Tropheryma whipplei*,[6] whilst Behçet's syndrome forfeited its place for many reasons including a lack of association with HLA-B27.[7]

Box 1 lists the seronegative spondarthritides currently recognized—now more commonly known as the seronegative spondylarthropathies or spondyloarthropathies.

Box 1 **The seronegative spondarthritides**

- Ankylosing spondylitis
- Reactive arthritis (Reiter's syndrome)
- Psoriatic arthropathy
- Enteropathic arthropathy
- Acute anterior uveitis
- Juvenile spondarthritis
- Undifferentiated spondarthritis
- Isolated peripheral enthesitis

PREVALENCE

The prevalence of HLA-B27 varies between populations—from 50% in Haida Indians to nil in Australian Aborigines. In the UK general population it is about 8%. HLA-B27 is rare in the American black population whereas Eskimo populations carry it much more frequently than Western Europeans, with prevalence rates of 25% or more.[8] This antigen is associated with ankylosing spondylitis in virtually all racial groups studied. In general, the population prevalence of ankylosing spondylitis parallels the frequency of HLA-B27. However, there is some variation in the strength of the association, which is weaker in native Indonesians, Lebanese, Thais and West Africans.[9]

In the UK, HLA-B27 is present in 90–95% of patients with ankylosing spondylitis, 60–90% of patients with reactive arthritis, 50–60% of patients with psoriatic arthritis or inflammatory bowel disease and spondylitis, and 80–90% of children with juvenile ankylosing spondylitis.

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STRUCTURE AND SUBTYPES

HLA-B27 is a MHC class I molecule consisting of an alpha chain encoded in the MHC region on chromosome 6 and a non-MHC encoded beta chain, β_2 microglobulin. 26 different alleles have been identified which code for 24 different proteins designated HLA-B*2701–B*2725 (B*2722 was deleted on the discovery that it had the same sequence as B*2706).[10] These allotypes differ from one another by a few aminoacid substitutions and the multiple alleles may have evolved from the most widespread subtype, B*2705. They vary in frequency among ethnic and racial groups and at least two of them, B*2706 in South East Asia and B*2709 in Sardinia, do not seem to be linked with ankylosing spondylitis.

ROLE IN AETIOPATHOGENESIS

In a European population study, ankylosing spondylitis was found in 1.3% of HLA-B27 positive individuals in the population at large and in 21% of HLA-B27 positive relatives of B27 positive patients with spondylitis, giving a 16-fold risk of ankylosing spondylitis in HLA-B27 positive relatives compared with B27 positive individuals in the general population.[11] HLA-B27 positive Caucasians have a 20-fold risk of developing any spondylarthropathy, particularly ankylosing spondylitis and undifferentiated spondarthritis.[12]

Family and twin studies of ankylosing spondylitis have shown a polygenic pattern of genetic susceptibility with heritability in excess of 90%. The contribution of HLA-B27 to genetic susceptibility has been estimated to be 20–50% of the total.[13] Other HLA alleles, most notably HLA-B60 and HLA-DR1, may predispose to ankylosing spondylitis either independently of B27 or in conjunction with it.[14] Homozygosity for HLA-B27 does not appear to enhance the risk of developing ankylosing spondylitis.[11]

Non-MHC susceptibility loci have been identified on other chromosomes,[15] whilst other HLA genes may have a protective effect against ankylosing spondylitis.[16] Thus, whereas HLA-B27 is almost essential for the development of ankylosing spondylitis, other genetic factors may determine which B27 carriers manifest disease. The gender bias in ankylosing spondylitis is not due to X-chromosome encoded genetic effects.[17]

PATHOGENETIC MECHANISMS

The main natural function of HLA-B27 is to form a complex with β_2 microglobulin which can bind short antigenic peptides such as those derived from intracellular micro-organisms. Following presentation at the cell surface, the complexes are specifically recognised by cytotoxic lymphocytes which then kill the infected cell.

Although early studies demonstrated an association between the presence of *Klebsiella pneumoniae* in the faeces and inflammatory activity in ankylosing spondylitis,[18] no organism has been convincingly shown to initiate idiopathic ankylosing spondylitis. However, organisms have been shown to trigger reactive arthritis, including *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Chlamydia*, *Mycobacteria* and possibly *Brucella*, all of which habitually survive intracellularly. HLA-B27 appears to enhance the invasion of *Salmonella* into intestinal epithelial cells.[19] It has proved difficult or impossible to find live bacteria or DNA in the joint but fragments of *Chlamydia*, *Yersinia* or *Salmonella* have occasionally been found in patients.[20,21]

Several theories have been proposed to explain the various ways in which HLA-B27 might predispose to spondarthritis (Box 2). Supporting evidence has been provided for some but not all. For example, HLA-B27 is capable of presenting potentially arthritogenic peptides to cytotoxic T lymphocytes and it also has unusual cell biology.[22] By contrast, the bacteria implicated in reactive arthritis have not been found to produce superantigens and there is little evidence to support antibody cross-reactivity or receptor-mediated mechanisms.[22] Although molecular mimicry has been described between an aminoacid sequence in HLA-B*2705 and *Klebsiella* and *Shigella* products, this exact aminoacid sequence is not found in HLA-B*2702 or B*2704 which are also disease-associated subtypes.[23] Strong evidence that it is HLA-B27 rather than a closely linked gene which is directly involved in pathogenesis is provided by rodents possessing HLA-B27 as a transgene, which can develop conditions similar to the spondarthropathies.[24]

The development of ankylosing spondylitis may be promoted by increased expression of HLA-B27 on the surface of peripheral blood mononuclear cells.[25]

OTHER DISEASE ASSOCIATIONS

Approximately 1% of people who are HLA-B27 positive develop acute anterior uveitis (AAU).[26] Overall, about 55% of cases of AAU are associated with an HLA-B27 positive serotype, rising to about 70% in patients with recurrent episodes of acute iritis.[27] 84% of HLA-B27 positive patients with AAU have other B27-associated diseases—specifically Reiter's syndrome, ankylosing spondylitis or psoriatic arthritis. Conversely, about 20–30% of patients with ankylosing spondylitis or Reiter's syndrome develop AAU.[28]

Of the two clinical forms of psoriasis, HLA-B27 is linked (along with HLA-Cw2) only to type II,[29] the late-onset variety which has a closer temporal association with arthritis.[30] In patients with psoriatic arthropathy, there is a strong association between HLA-B27 and palmoplantar pustulosis whilst scalp psoriasis may occur less frequently in patients with B27.[31]

Box 2 **Mechanisms proposed to explain association of HLA-B27 with spondarthritis**

Hypothesis	*Putative mechanism*
Thymic selection of T cell repertoire	Selection of population of arthritogenic T cells
'Arthritogenic peptide'	HLA-B27 restricted cytotoxic T cell response to a peptide in joint tissues
Unique biological properties	Certain biochemical or cell biological features of HLA-B27 may predispose to disease development
'Altered self'	Unpaired cysteine residue at position 67 might modify immunogenicity or cell biology of HLA-B27
HLA-B27 derived peptides may be presented by HLA class I or II molecules	Certain HLA class II restricted T cells stimulated by bacterial infection might have cross reactive specificity for an HLA-B27 derived peptide presented by host cells
Interaction with microbial superantigens	Although not described for MHC class I antigens, it is possible that HLA-B27 specific superantigens could exist
Molecular mimicry	Disease may result from a cross-reactive antibody response between a unique portion of HLA-B27 and certain bacterial epitopes
Receptor hypothesis	Micro-organisms could recognize specific MHC molecules and use them as a vehicle by which to enter the cell
Linkage to disease-associated gene	HLA-B27 could merely be a marker for a linked disease-associated gene

Upper lobe fibrosis is the lung condition best known to correlate with HLA-B27. The antigen may be positively,[32] neutrally[33] or negatively[34] associated with asbestosis. Contradictory claims have also been made for an association with other pulmonary diseases, especially pleurisy, pleural abscess, bronchitis and pneumonia and pneumothorax, independently of the presence of ankylosing spondylitis.[35,36]

Aortic regurgitation occurs in 2–10% of patients with ankylosing spondylitis, and cardiac conduction abnormalities including atrioventricular and intraventricular blocks have been found in one-third of patients with spondylitis.[37] HLA-B27 related cardiac lesions may be found in the absence of other rheumatological manifestations. Indeed, an HLA-B27 associated cardiac syndrome comprising severe cardiac conduction system abnormalities and lone aortic regurgitation has been defined, whose link with B27 is almost as strong as that between B27 and ankylosing spondylitis.

An increased risk of leukaemia in ankylosing spondylitis has been attributed to therapeutic spinal irradiation, which consequently fell from favour three decades ago. However, a significant association has been reported between HLA-B27 and acute leukaemia, particularly acute myeloid leukaemia.[38] HLA-B27 carriers may have an increased risk of acute leukaemia whilst those with concomitant ankylosing spondylitis may be predisposed to lymphoid malignancies.

While infection with HIV predisposes to spondyloarthropathy,[39] HLA-B27 is the HLA class I molecule most closely associated with non-progression of HIV infection to AIDS.[40]

DIAGNOSTIC UTILITY

As the population prevalence of HLA-B27 in the UK is approximately 8% and only around 1% of B27 positive individuals develop ankylosing spondylitis, screening the general population for the antigen would not be helpful for identifying cases of spondylitis. The predictive value of testing for HLA-B27 depends upon the particular clinical situation. Beginning with a clinical estimate of the likelihood of ankylosing spondylitis or a related spondarthropathy, Bayes' theorem can be used to calculate the probability that a patient has the disease, depending on whether they transpire to be HLA-B27 positive or negative.[41] The usefulness of a positive result will be greatest in populations, such as the Japanese, that have a low general prevalence of HLA-B27 and yet its association with ankylosing spondylitis is strong. For the other spondarthritides, which are less strongly linked with HLA-B27, diagnosis is based primarily on the associated clinical features.

Thus, in practice, typing for HLA-B27 can be helpful in a patient complaining of low back pain of an inflammatory character in the absence of radiological signs of sacroiliitis or in patients with an asymmetrical oligoarthritis but without other features of spondarthritis. This has been acknowledged with the inclusion of HLA-B27 positivity as a criterion in the Amor classification criteria for spondyloarthropathy.[42]

Likewise, testing for HLA-B27 can help to differentiate between alternative aetiologies in iritis and aortic regurgitation.

PROGNOSTIC VALUE

Whereas HLA-B27 does not seem to influence the severity of ankylosing spondylitis,[43] in psoriatic spondylarthropathy it may determine not only susceptibility to the condition but also its clinical expression.[44] It correlates most strongly with isolated axial disease and it may confer some protection against peripheral joint erosions.

Patients with Reiter's disease and *Yersinia* and *Salmonella* triggered reactive arthritis who are HLA-B27 positive have more severe acute disease, more extra-articular features and more frequent chronic back pain and sacro-iliitis.[45,46] In *C. trachomatis* reactive arthritis, more severe or chronic disease could be due to lower concentrations of interferon-γ in the synovial fluid of patients who are HLA-B27 positive than those who are HLA-B27 negative, with consequent impaired clearance of infective agents.[47]

With regard to cardiac disease, the relative risk that a HLA-B27 positive man will need a permanent pacemaker has been calculated to be 6.7 compared with a man who has other B alleles.[37] This association is not, however, present in female patients.

A poor outcome of back surgery has been found in patients possessing HLA-B27.[48] Whether this was because a substantial number of patients operated on had spondarthritis rather than mechanical back pain, or because HLA-B27 predisposes to a poor outcome in back surgery, was not clear.

Atlanto-axial subluxation can occur in both rheumatoid arthritis and ankylosing spondylitis. Compared with HLA-B27 negative patients, HLA-B27 positive patients with rheumatoid arthritis have about twice the risk of developing subluxation of the cervical spine and an almost threefold risk of subaxial subluxation.[49,50] Thus, HLA-B27 may transpire to be a useful prognostic indicator for the later development of instability of the cervical spine and its complications in rheumatoid arthritis.

CONCLUSION

The discovery of the link between HLA-B27 and a large family of inflammatory rheumatic diseases was one of the seminal advances in rheumatology in the last century. Associations have subsequently been identified with other musculoskeletal and non-rheumatic diseases. The distinction

between the disease-associated and non-associated subtypes may give an insight into precisely how HLA-B27 contributes to pathogenesis in the seronegative spondarthritides, whilst some of the pathogenesis hypotheses may help to elucidate the mechanisms of disease susceptibility, initiation and progression. New ways to employ HLA-B27 as a diagnostic and prognostic aid will continue to emerge.

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